REMARKS

A. Request for Suspension Under 37 C.F.R. § 1.103(c)

Applicants hereby request suspension of action by the Office for a period of three months as provided by 37 C.F.R. § 1.103(c). Pursuant to the requirements under § 1.103(c), this request is accompanied by a Request for Continued Examination and the fees required under 37 C.F.R. § 1.17(e) and 1.17(i). The Applicants contemplate submission of additional evidence, e.g., in the form of a Rule 132 declaration, during the period of suspension.

B. Status of the Claims

New claims 108 and 109 have been added and claims 1-83 and 93 are canceled. Support for new claim 108 can be found, at least in Table 6 on page 30. Support for claim 109 can be found at least in Table 6 on page 30, Table 2 on page 20 and Table 3 on page 21. In view of the amendments, claims 84-92 and 94-109 are currently pending in the case.

C. Rejections Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

The Examiner rejected claims 84-92 and 94-107 for lack of adequate written description, alleging excessive scope of the genus of peptide substrates for use in the assay methods recited in the claims.

However, the Action overstated the variation of peptide substrate cleavage motifs recited in the instant claims. The claims concern methods of assaying for modulators of β-secretase activity and recite a genus of peptide substrates comprising at least six amino acids that represents a finite number of peptide sequences. The Examiner points to the alleged immense scope of the claims by stating that given the general formula for a peptide substrate described in Table 6 of the application there would be 9,878,400 individual members of the genus of substrates. Even if the size of the genus is 9.8 million, the genus of substrates outlined to by the Examiner is not large in the fields of chemistry and molecular biology, in view of the high through-put screening techniques that are used in these fields.

Nonetheless, the Examiner's analysis of genus size with respect to the table in the application is irrelevant *with respect to the current claims*, wherein the identity of three of the four amino acid positions surrounding an aspartyl cleavage site are specifically defined by one residue, and a fourth amino acid is limited to six choices. Thus, substrate peptides of at least six amino acids currently recited in the claims concern only six permutations at the more important P_2P_1-$P_1'P_2'$ positions of the substrate, and only about 2,400 individual 6-mer sequences. The breadth of such a claim can hardly be considered excessive considering the field of the invention and state of the art at the time that the application was filed. For example, in biotechnology patent applications, claims often concern polypeptide sequences that are defined by percent identity to a given polypeptide sequence. For example, a claim concerning a polypeptide having at least 99% identity to a 300 amino acid polypeptide concerns about 214 billion individual member sequences (assuming a standard 20 amino acid repertoire at a given position). (The Patent Office, of course, routinely allows claims with 95% identity, which increases – by many orders of magnitude – the number of sequences embraced by the genus of 99% identity.) Thus, in view of the technical field and the comparatively narrow scope of the current claims, it was improper to characterize the claims in this application as overly-broad.

Furthermore, the Examiner understated the teachings of the application regarding the amino acid sequences that may be used as peptide substrates in methods of the invention. Specifically, the Examiner alleges that Applicants fail to "provide a structure-activity nexus linking the broad array of species," (page 7 of the March 27, 2007 Action). To the contrary, the teachings of the specification *specifically* provide a structure-activity nexus regarding the substrate peptides. For example, the instant application describes each substrate amino acid position in detail disclosing specific preferred and high preferred residues that may be used at each position (for achieving desired "substrate activity") and further describes the general properties of residues that should be used at each position.

The application also provides clear teachings with respect to the genus currently claimed. The instant claims concern in some aspects, a peptide comprising the sequence P_2P_1-$P_1'P_2'$ wherein P_2 is N, P_1 is Y, L, M, Nle, F or H, P_1' is E and P_2' is V. The specification clearly teaches such a genus. For instance, the paragraph spanning pages 21-22 teaches an optimized peptide wherein P_1' and P_2' are E and V respectively, and it is taught

that "substitution of the P_2 Thr with Asn [N] generated a peptide...with activity similar to that of the Swedish mutant," (page 22). Furthermore, the specification teaches that P_1 should be "an aromatic amino acid or a aliphatic amino acid," or "in preferred, embodiments, P_1 is an amino acid selected from the group consisting of Y, L, M, Nle, F and H," (pages 3 and 5 of the specification, respectively). The specific structural definitions of the substrates are based in part on the functional studies described in the examples and the application clearly teaches the importance of particular amino acid properties at each position in a peptide substrate.

Studies described in the specification demonstrate that multiple members of the claimed genus of peptide substrates are cleaved by a human aspartyl protease activity and thus may be employed in the claimed assays (see, *e.g.*, SEQ ID NOS:5, 133, 134, 135 and 136 in Tables 2 and 3). Thus, the peptide substrates defined in the claims are clearly structurally and functionally defined in the application and thus a nexus between structure and function of the peptides has been clearly established contrary to the arguments made by the Examiner.

When the Patent Office disputes written description support for a claimed invention, it is incumbent upon the Examiner to present evidence and reasoned argument as to why support for the claims is doubted. The Applicants have already demonstrated that any reasoning or evidence cited in this case is unpersuasive. The Examiner cited a number of references that were alleged to demonstrate an insufficiency in the teachings of the instant application. Specifically, the Examiner cited Gruninger-Leitch *et al.* (2002), Majer *et al.* (1997), Sauder *et al.* 2000, Shi *et al.* (2005) and Tomasselli *et al.* (2003), and argued that the references show peptide substrates with a variety of substitutions show *decreased* cleavage by aspartic proteases and thereby demonstrate that the genus of substrate peptides are insufficiently defined in the instant application. However, no reference cited by the Examiner exemplifies a substrate peptide within the claimed genus that is *inoperative*. While some substrates of the cited references may be non-optimal they can not be characterized a inoperative. Thus, none of the references cited by the Examiner support the instant rejection. Moreover, it is not the function of the claims to specifically exclude possible inoperative embodiments. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co. and Alamo Explosives* Co. Inc. 750 F.2d 1569, 1576 (Federal Circuit 1984).

The Examiner specifically asserts that the application fails to support claims concerning substrate peptides wherein P_1 is M, F or H. However, as summarized above, the specification specifically teaches that "in preferred, embodiments, P_1 is an amino acid selected from the group consisting of Y, L, M, Nle, F and H," (page 5 of the specification). The Examiner has failed to identify why the skilled artisan would not recognize such substrates as part of the invention despite the specific disclosure of the specification.

According to the United States Patent and Trademark Office Revised Interim Written Description Guidelines, the specification provides an adequate written description of a genus if a *representative* number of species are implicitly or explicitly disclosed. It is undisputed that all members of the claimed genus are explicitly disclosed in the application, e.g., in the Table, and the analysis above shows that the claimed genus also is specifically disclosed.

Furthermore, the application exemplifies the functionality (as substrates) of a representative number of the species in the genus. Specifically, the specification demonstrates that peptides comprising an L (SEQ ID NO:133), Nle (SEQ ID NO:134), Y (SEQ ID NO:5) (as recited in claim 108) or M (*e.g.*, the natural APP sequence) at the P_1 position are cleaved by an aspartyl protease.

The references cited by the Examiner further support the sufficiency of the teachings in the application. Specifically, while none of the references demonstrate any peptide in the claimed genus that is non-functional, the references do exemplify the functionality of additional members of the claimed genus. For example, in Shi *et al.* (2005) Applicants competitor demonstrates that peptides comprising an F at the P_1 position are cleaved very efficiently by aspartyl protease activity (see, *e.g.*, figure 2 on page 143). Thus, the specification provided explicit support for the claimed genus and provides functional data for a representative number of species in the claimed genus.

The Rejection has mischaracterized the claims as overly-broad and has understated the teachings of the specification. No evidence has been provided that shows why a skilled artisan would question Applicants' possession of the claimed invention or the sufficiency of the teachings provided in the application. To the contrary, references cited by the Examiner demonstrate that the teachings provided in the specification were adequate since peptide substrates defined in the claims are functionally cleaved by aspartic protease

activity. In view of the foregoing the rejection of claims 84-92 and 94-107 for alleged lack of adequate written description should be withdrawn.

D. Double Patenting Rejections Should be Withdrawn

Claims 84-92 and 94-107 were provisionally rejected under 35 U.S.C. § 101 as claiming the same subject matter of claims 84-107 of co-pending application nos. 10/801,487, 10/801,493, 10/801,938, claims 43, 49, 58-60, 64 and 66 of co-pending application no. 10/801,486 (now abandoned) and claims 102-131 of co-pending application no. 09/908,943 (now U.S. Patent No. 7,205,120). However, the claims in the cited applications and patent are not identical in scope to the claims at issue. Thus, the provisional double patenting rejection is inappropriate and should be withdrawn.

Conclusion

Examiner is invited to contact the undersigned at the number provided with any questions.

Dated: October 31, 2007

Respectfully submitted,

/David A. Gass #38153/ David A. Gass
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant